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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/284,009	04/05/1999	CLAIRE E. LEWIS	550-128	1771

7590 11/21/2003

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EXAMINER	
QIAN, CELINE X	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/284,009	LEWIS ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *87-93,101,104,109-116 and 120-125* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *87-93,101,104,109-116 and 120-125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4/5/99* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0803*.
4) ☒ Interview Summary (PTO-413) Paper No(s). *1003*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 87-93, 101, 104, 109-116 and 120-125 are pending in the application.

This Office Action is in response to Amendment filed on 8/11/03.

Response to Amendment

The rejection of claims 87-93, 101, 104, 109-116 and 120-125 under 35 U.S.C.112 1st paragraph is maintained for reasons set forth of the record mailed on 3/11/03 and further discussed below.

Claims 89-93, 109 and 110 are rejected under 35 U.S.C.112 2nd paragraph for reasons discussed below.

Claim 123 is objected to for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 87-93, 101, 104, 109-116 and 125 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a mononuclear phagocyte modified to comprise at least one regulatable element operably linked to at least one nucleotide sequence of interest (NOI), wherein said regulatable element is selected from a hypoxia regulatable element, an ischemic regulatable element and a stress regulatable element, and wherein the NOI is a marker gene or reporter gene; a delivery system comprising said mononuclear phagocyte; a construct comprises at least one regulatable element operably linked

to at least one nucleotide sequence of interest (NOI), wherein said regulatable element is selected from a hypoxia regulatable element, an ischemic regulatable element and a stress regulatable element, and wherein the NOI is a marker gene or reporter gene; and a method of internalizing said construct into a mononuclear phagocyte, does not reasonably provide enablement for such mononuclear phagocyte comprising a regulatable element selected from hypoxia, ischemic and stress element, operably link to any type of NOI. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Claims 120-124 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to the rejection, Applicants argue that the data described in example 1 and 2 of the Naylor declaration support that the methods and results described in the present application are enabling in an *in vivo* situation. Naylor declaration further states that the replacement of a reporter gene with a therapeutic gene would be a matter of routine experimentation as it refers in this regard to U.S. Patent No.6,265,390. The declaration also demonstrates the expression of HIF-1α in the macrophages when exposed to hypoxia *in vitro* or in avascular areas of human tumors, wounds and arthritic joints. Dr. Naylor thus concludes that hypoxic condition can induce the activity of hypoxia inducible transcription factors that is capable of binding to cognate DNA recognition sites and upregulating the expression of a gene of interest. Applicants assert that the Naylor declaration is persuasive and conclusive as to the

enablement of use of mononuclear phagocyte to deliver a drug, or therapeutic gene, to a hypoxic site to achieve a therapeutic effect. Applicants further refers to U.S. Patent No. 6,379,647, Nishihara et al., Kluth et al. as support for the ability of mononuclear phagocyte to target hypoxic or ischemic sites. Finally, Applicants argue that although the references are published after the filing date of the current application, it should be considered because the MPEP allows for applicant to rely on such art when a testimony of an expert based on the publication as evidence of the level of skill in the art at the time of filing is offered.

These arguments has been fully considered but deemed unpersuasive. The reasons for non-enablement of the claimed invention were discussed in detail in the office action mailed on 8/26/02 and 3/11/03. The Naylor declaration has been fully considered. Applicants are reminded that the non-enablement rejection is not based on how to make a vector comprising a therapeutic gene but on how to achieve high and sustained level of expression of the therapeutic gene *in vivo*, hence achieve a therapeutic effect. The technical difficulties of cell based gene therapy has been discussed in detail in the office actions mailed on 8/26/02 amd 3/11/03. Neither the specification, nor the Naylor Declaration provides sufficient teaching to overcome these difficulties. The Naylor Declaration only supports the enablement of deliverying a marker gene to hypoxic site in vivo. Although patent 6,265,390 gives example of transfecting constructs comprising hypoxia regulating element *in vitro*, it fails to demonstrate a therapeutic effect of the gene expression *in vivo*. Therefore, the invention is only enabled for a mononuclear phagocyte that delivers a marker gene or reporter gene to a hyoxic, ischemic or stress site.

The MPEP 2164.05 (a) states that the invention must be enabling as of the filing date. It further states: "The state of the art existing at the filing date of the application is used to

determine whether a particular disclosure is enabling as of the filing date. Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); In re Budnick, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976) (In general, if an applicant seeks to use a patent to prove the state of the art for the purpose of the enablement requirement, the patent must have an issue date earlier than the effective filing date of the application.). While a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed. Gould v.Quigg, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987)."

According to this standard, none of the references cited by Applicants such as 6,379,647, Nishihara et al., and Fluth et al. is able to support the enablement of claimed invention at the time of the invention was made. The priority date of the instant application is 10/9/1996, all of these references were made public after this date. The declaration by Dr. Naylor is at most based on 6,295,390, not the rest of the references. However, the US 6,295,390 does not support the enablement of a phagocyte comprising a therapeutic gene for reasons discussed above. Therefore, these references cannot be used to show what was known at the time of filing, thus to make up the insufficient disclosure of the instant specification. As such, the claimed invention is not enabled to its full scope at the time of the filing.

During the interview conducted on 10/2/03, Applicants' representative argues that the based on the disclosure and the Declaration, the invention is enabled for a mononuclear

phagocyte comprising a hypoxic regulating element for delivering a reporter or a marker gene. This argument has been fully considered, and the claimed invention is enabled for a mononuclear phagocyte modified to comprise at least one regulatable element operably linked to at least one nucleotide sequence of interest (NOI), wherein said regulatable element is selected from a hypoxia regulatable element, an ischemic regulatable element and a stress regulatable element, and wherein the NOI is a marker gene or reporter gene; a delivery system comprising said mononuclear phagocyte; a construct comprises at least one regulatable element operably linked to at least one nucleotide sequence of interest (NOI), wherein said regulatable element is selected from a hypoxia regulatable element, an ischemic regulatable element and a stress regulatable element, and wherein the NOI is a marker gene or reporter gene; and a method of internalizing said construct into a mononuclear phagocyte.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 89-93, 109 and 110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 89-93, the recitation of "wherein the mononuclear phagocyte further comprises a binding agent capable of" renders the claims indefinite because it is unclear where the binding agent is located.

Regarding claim 109, the recitation of "a delivery system for targeting a mononuclear phagocyte...and a stress site" renders the claim indefinite because it is unclear what is the nature

of said delivery system. It is unclear whether is a mononuclear phagocyte, a construct, or some other delivery composition. As such, the metes and bounds of the claim cannot be established.

Claim 110 recites the limitation "hypoxia, ischemic or stress" in line 1 and 2. There is insufficient antecedent basis for this limitation in the claim. The parent claim (87) does not have such limitation.

Claim Objections

Claim 123 is objected to as being dependent upon a cancelled base claim (96). Applicant is advised to rewrite the claim in independent form including all of the limitations of (canceled) base claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is 703-305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Anne-marie Falke

ANNE-MARIE FALKE, PH.D
PRIMARY EXAMINER

Celine Qian, Ph.D.